Remarks

Claims 55-65 remain in this application. Applicants respectfully request entry of the amendments, reconsideration by the Examiner, and advancement of the application to allowance.

Formal Matters

Claims 55-65 were subject to restriction in Paper No. 5, mailed 1/29/03. Upon reconsideration, the Examiner has decided to withdraw the restriction requirement and examine all pending claims.

Title

The Examiner has objected to the title of the invention as not being descriptive. The Examiner requests amending the title to be clearly indicative of the invention to which the claims are directed. Accordingly, applicants have amended the title to be indicative of the invention to which the claims are directed.

35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 60, 61 and 64 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended claims 60 and 61 to improve the form of the claims. Accordingly, applicants respectfully request that the rejection of claims 60, 61 and 64 be withdrawn.

In addition, claim 65 as originally written includes an obvious typographical error. Therefore, applicants have amended claim 65 to improve the form of the claim.

35 U.S.C. § 102(e)

The Examiner rejected claims 55-65 under 35 U.S.C. § 102(e) as being anticipated by Hoffman et al. (U.S. Pat. No. 5,409,825) and Emerson et al. (U.S. Pat. No. 6,326,198). The Examiner notes that Hoffman et al. disclose stem cells obtained from native IL-3/GM-CSF fusion proteins while Emerson et al. disclose stem cells obtained from the combination of IL-3 + GM-CSF. The Examiner further notes that absent evidence to the contrary, the stem cells in Hoffman et al. and Emerson et al. are identical to the claimed stem cells obtained from mutant IL-3/GM-CSF fusion proteins.

Applicants submit evidence showing that the claimed stem cell population obtained are not expected to be identical to the stem cell population of the prior art. Attached to this response is a published paper by Abregg et al. (*The Enhanced in vitro Hematopoietic Activity of Leridistim, A Chimeric Dual G-CSF and IL-3 Receptor Agonist*, Leukemia 16:316-326 (2002)) in which differences between stem cell populations are displayed. In particular, the resulting stem cell population obtained from leridistim (one member of a family of related mutant IL-3. fusion proteins), exhibit differences as compared to stem cells obtained from G-CSF, IL-3 or G-CSF + IL-3 (as best seen in Tables 4A and 4B). Cells were classified as myelocytes/promyelocytes (immature neutrophils; $CD15^+/CD11b^-$), metamyelocytes (mature neutrophils; $CD15^+/CD11b^+$), blast cells ($CD15^-/CD11b^-$) and monocyte/macrophage precursors ($CD15^-/CD11b^+$). On day 5 of *ex vivo* culture using peripheral blood CD34+ cells, the progenitor cell population (CD34+/CD15./CD11b.) comprised the greatest number of cells for

each culture condition (Table 4A). Cultures treated with leridistim, SC-65303, or rhG-CSF and SC-65303 in combination contained monocyte/macrophage precursors whereas there were much lower levels of these cells present in the rhG-CSF cultures. The number of immature neutrophils on day 5 was found to be two- to three-fold greater in the leridistim and the rhG-CSF and SC-65303 combination cultures than in the SC-65303 cultures. More profound differences were observed when leridistim or the rhG-CSF and SC-65303 combination cultures were compared with rhG-CSF cultures (56- and 58-fold greater, respectively). On day 5, greater numbers of mature neutrophils were observed in the leridistim cultures than in cultures with other cytokines. Similar data were obtained for the effect of leridistim on 5 day culture of bone marrow derived cells (Table 4B). These data suggest that on day 5, leridistim treatment of CD34+ cells from PBPC and BM results in expansion of cells with immature and mature neutrophil characteristics. On day 12, dramatic differences were noted in the distribution of granulocytic precursor cells during *ex vivo* culture of PBPC and BM cells. At day 12, culture of PBPC CD34 cells with leridistim promoted expansion of cells displaying the mature neutrophil phenotype; 13- and 22-fold greater expansion than in the cultures treated with the combination of rhGCSF and SC-65303, or SC-65303, respectively, and 1131-fold greater than with rhG-CSF. Culture with leridistim, SC-65303, or a combination of rhG-CSF and SC-65303 increased the cells displaying the immature neutrophil cell phenotype 409-, 118- and 123-fold, respectively, over that attained with rhG-CSF treatment. Blast cells and monocyte/macrophage precursors were present in the cultures containing leridistim, SC-65303, or the combination of rhG-CSF and SC-65303 at

signi.cantly higher levels than within rhG-CSF cultures. On day 12, BM CD34cells cultured with leridistim demonstrated a dramatic increase in mature neutrophils (707-, 204- and 11.5-fold greater expansion compared to that resulting from rhG-CSF, SC-65303, or the combination of rhGCSF and SC-65303, respectively) (Table 4B). Morphological assessment of CD15/CD11bcells sorted by FACSVantage and stained by Wright–Giemsa showed the characteristic segmented lobes of mature neutrophils (data not shown). The monocyte/macrophage precursor cells were present at higher levels in cultures containing both receptor agonists (ie leridistim or rhG-CSF in combination with SC-65303). Blast cells were present at significantly higher levels in the cultures containing leridistim, SC-65303, or the combination of rhG-CSF and SC-65303. These results suggest that by day 12, leridistim treatment of both PBPC and BM cells induces greater expansion of cells with the mature and immature neutrophil phenotype than the other treatments.

Thus, the claimed stem cell population produced by mutant IL-3 fusion proteins are different than those disclosed in the prior art. Accordingly, applicants respectfully request that the rejection of claims 55-65 under 35 U.S.C. §102(e) be withdrawn and claims 55-65 be allowed.

In addition, the Examiner requests that the limitations recited in previous United States patents that are parents of this application be incorporated into the claims of the present application. Therefore, in order to facilitate prosecution, applicants have amended independent claims 55, 57 and 58 to incorporate the limitations recited in previous United States patents that

are parents of the present application. However, applicants maintain the claimed stem cells produced by the mutant IL-3/GM-CSF fusion molecules are fully enabled by the specification and are not taught or suggested in the prior art.

35 U.S.C. § 103

The Examiner rejected claims 55-65 under 35 U.S.C. § 103 as being unpatentable over Hoffman et al. (U.S. Pat. No. 5,409,825) or Emerson et al. (U.S. Pat. No. 6,326,198) in view of Curtis et al. (WO 91/02754). The Examiner states neither Hoffman et al. nor Emerson et al. specifically teach the use of a native IL-3/GM-CSF fusion protein alone in producing stem cells. The Examiner notes that Curtis et al. teaches a IL-3/GM-CSF fusion protein that is more biologically active than either of the two proteins alone. The Examiner states therefore it would have been obvious to substitute the fusion protein in Curtis et al for the combination of fusion protein and MGF in Hoffman et al. or the IL-3 and GM-CSF proteins in Emerson et al. since this would guarantee simultaneous administration of these proteins to the stem cell.

To establish a *prima facie* case of obviousness, the USPTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated one of ordinary skill in the art to modify a reference or combine references. Second, the proposed modification must have had a reasonable expectation of success. Finally, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *See* MPEP §2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As noted above, Hoffman et al., Emerson et al., and Curtis et al. neither teach nor suggest stem cells obtained from mutant IL-3/GM-CSF fusion proteins as claimed in the present application. Accordingly, Applicants request that the rejection of claims 55-65 under 35 U.S.C. §103 be withdrawn and claims 55-65 be allowed.

Conclusion

In view of the foregoing remarks, Applicants respectfully submit that this application and all pending claims are in condition for allowance, and such is requested.

This Amendment does not increase the number of independent claims, does not increase the total number of claims, and does not present any multiple dependent claims. Accordingly, no fee based on the number or type of claims is currently due.

Applicants submit a check in the amount of $110.00 for the fee for a one (1) month extension of time. Applicants hereby authorize the Commissioner to charge any additional fees that may be required by this paper to Deposit Account 07-0153.

Respectfully submitted,

Date: 9/19/03

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Attorney Docket No. 126181-1038